Stroke and death in elderly patients with atrial fibrillation in Japan compared to the United Kingdom

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Stroke and death amongst elderly patients with atrial fibrillation: A comparative analysis of Japan and United Kingdom subjects

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Abstract:	Data on stroke, mortality and associated comorbidities in elderly atrial fibrillation (AF) patients in Japan may differ from Western countries. There has never been a systematic comparison between stroke risk profiles and outcomes amongst community-based elderly patients with AF in Japan and the United Kingdom (UK). Objective and Methods: We compared clinical characteristics, stroke risk and outcomes amongst elderly AF patients from the Fushimi AF Registry (Japan; N=1791) and the Darlington AF registry (UK; N=1338). Results: The Fushimi cohort had a mean age 81.8 years and CHA2DS2-VASc score 4.3(1.4), whereas the Darlington cohort had a mean age 83.6(5.7) years and CHA2DS2-VASc score 4.4(1.4). Over a 12 month follow-up period, observed stroke and mortality rates in Fushimi were 3.4%(n=61) and 11.5%(n=206), whilst corresponding event rates in the Darlington cohort were 4.4%(n=59) and 14.1%(n=188), respectively. Appropriate use of oral anticoagulation (OAC, essentially vitamin K antagonist) was <60% in both registries. On multivariable analysis, ethnicity (Japan vs.UK) was neither associated with the risk of stroke (Odds Ratio[OR] 0.92, 95%CI 0.63-1.36; p=0.69) nor death(OR 0.92, 95%CI 0.80-1.27; p=0.92). In a subgroup analysis of elderly patients not receiving OAC(n=1489), a prior history of stroke was associated with the risk of stroke(OR 2.42; 95%CI 1.39–4.12; p=0.002),

	but not ethnicity(OR 0.86; 95%CI 0.50-1.47; p=0.58). Conclusions: Elderly(age≥75) AF patients in both Japan and the UK are at similarly high risk of stroke and death, with OAC still under-utilised in both populations. Ethnicity was not independently associated with the risk of stroke, regardless of OAC use or non-use.

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Declarations of Interest

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Abstract

Background: Data on stroke, mortality and associated comorbidities in elderly atrial fibrillation (AF) patients in Japan may differ from Western countries. There have been few systematic comparisons between stroke risk profiles and outcomes amongst community-based elderly (aged ≥75) patients with AF in Japan and the United Kingdom (UK).

Objective and Methods: We compared clinical characteristics, stroke risk and outcomes amongst elderly AF patients from the Fushimi AF Registry (Japan; N=1791) and the Darlington AF registry (UK; N=1338).

Results: The Fushimi cohort had a mean age 81.8 (SD 5.3) years and CHA_2DS_2-VASc score 4.3 (1.4), whereas the Darlington cohort had a mean age 83.6 (5.7) years and CHA_2DS_2-VASc score 4.4 (1.4). Over a 12 month follow-up period, observed stroke and mortality rates in Fushimi were 3.4% (n=61) and 11.5% (n=206), whilst corresponding event rates in the Darlington cohort were 4.4% (n=59) and 14.1% (n=188), respectively. Appropriate use of oral anticoagulation (OAC, essentially a vitamin K antagonist) was <60% in both registries. On multivariable analysis, ethnicity (Japan vs. UK) was neither associated with the risk of stroke (Odds Ratio [OR] 0.92, 95%CI 0.63-1.36; p=0.69) nor death (OR 0.92, 95%CI 0.80-1.27; p=0.92). In a subgroup analysis of elderly patients not receiving OAC (n=1489), a prior history of stroke was associated with the risk of stroke (OR 2.42; 95%CI 1.39–4.12; p=0.002), but not ethnicity (OR 0.86; 95%CI 0.50-1.47; p=0.58).

Conclusions: Elderly (age≥75) AF patients in both Japan and the UK are at similarly high risk of stroke and death, with OAC still under-utilised in both populations. Ethnicity was not independently associated with the risk of stroke, regardless of OAC use or non-use.

Keywords Ethnicity, Stroke, Death, Aged, Atrial fibrillation

KEY MESSAGES

What is already known about this subject?

Data on stroke, mortality and associated comorbidities in elderly atrial fibrillation (AF) patients in Asia may differ from Western countries. There is the perception that risk factors for stroke and outcomes amongst Japanese patients with AF may differ from those in Western countries.

What does this study add?

Both Japan and UK cohorts are at similarly high risk of stroke and death. Oral anticoagulation (OAC) was under-utilised (<60%) in both populations, despite a lower risk of death being significantly associated with OAC use. Ethnicity (Japanese vs. British) was not independently associated with the risk of stroke regardless of whether or not OAC was used.

How might this impact on clinical practice?

Our results can inform specific guidance on the implications of different stroke risks and profiles in Asians vs Caucasians, and highlight considerable gaps between AF treatment guidelines and clinical practice in Asians as well as Caucasians, in particular, the underuse of OAC. Moreover, the perception that individuals of Asian ethnicity are at higher risk of stroke than Caucasians should be reconsidered given that our results demonstrate no obvious ethnic difference between Asians and Caucasians in the risk of stroke.

Introduction

Age is an important determinant of stroke risk in atrial fibrillation (AF), which independently increases the risk by 1.5-fold per decade of life among patients with AF.[1] Nonetheless, data on stroke and thromboembolism in elderly patients in Japan are limited, which is important given the increasing elderly age profile of the general population in Japan. Furthermore, there is the perception that risk factors for stroke and outcomes amongst Japanese patients with AF may differ from those in Western countries. However, there have been few systematic comparisons between risk profiles and outcomes amongst community-based elderly (age >75) patients with AF in Japan and United Kingdom (UK). [2]

To investigate this further, we used the Fushimi AF Registry as a Japanese community-based population and the Darlington AF registry as a UK community-based population to evaluate ethnic differences in clinical characteristics, stroke risk profiles and outcomes amongst elderly AF patients in Japan and the UK.

Methods

The design of Fushimi AF Registry has been previously described. [3 4] In brief, the Fushimi AF Registry is a community-based prospective survey of AF patients in Fushimi-ku, Kyoto. Fushimi-ku is densely populated with a total population of 283,000, and is assumed to represent a typical urban community in Japan. A total of 79 institutions, all of which are members of Fushimi-Ishikai (Fushimi Medical Association), participated in the registry. The enrolment of patients started in March 2011. A total of 3,499 patients were enrolled by April 2014, with 51% being aged >75 (n=1,791) and 100% were Japanese. The Fushimi AF Registry (UMIN Clinical Trials Registry: UMIN000005834) protocol was approved by the ethical committees of the National Hospital Organization Kyoto Medical Center and Ijinkai Takeda General Hospital.

The design of the Darlington AF registry has also been described previously.[5] In brief, the study population was derived from all 105,000 patients who were registered at one of 11 general practices serving the town of Darlington. All patients whose vital status in March 2013 was known were eligible for inclusion. A total of 2,259 (2.15%) patients with AF were identified (59% were aged >75, n=1338), using the Guidance on Risk Assessment in Stroke Prevention for Atrial Fibrillation (GRASP-AF) tool [6] and are included in this analysis. According to the last Census data in the Darlington cohort, more than 96% of the Darlington population were Caucasian. For the Darlington registry, ethical approval was not required under United Kingdom National Health Service research governance arrangements for the project.

Baseline clinical characteristics of the subjects entered in the Fushimi AF Registry and Darlington AF Registry have also been reported elsewhere.[3 5] Patients were categorised according to the CHA_2DS_2-VASc scores (Congestive heart failure, Hypertension, Age ≥ 75 years [double], Diabetes mellitus, previous thromboembolism [double], Vascular disease, Age 65–74 years, and female gender). The primary endpoints in the present analysis were the incidence of stroke and all-cause death during the follow-up period. In the present study, we used the data of all patients with obtainable follow-up information in the Fushimi AF Registry, and those registered in the Darlington AF registry. We extracted and compared the data of elderly AF patients (aged≥75) from both registries.

Differences in the methods of data collection among the two databases were seen. The Darlington AF Registry was a completed study that dealt with a closed cohort and had 100% follow-up data. In contrast, the Fushimi AF Registry was an on-going cohort, with enrolment on-going at the time of the present analyses. Therefore, to ensure an equivalent period for the two databases, we analysed the follow-up data at 12 months.

Statistical analysis

Categorical and continuous patient data are presented as number (%) and mean ± SD, respectively. The incidence of ischemic stroke was presented as actual number and percentages of patients according to the CHA_2DS_2-VASc scores. Multivariate logistic regression analysis was performed to determine the independent risk factors for ischemic stroke and all-cause death after adjusted for components of the CHA_2DS_2-VASc score (age assessed as a continuous variable) and use of antithrombotic agents. The relatively homogeneous ethnicity make-up of the two registry cohorts allows inter-ethnic

comparisons. All statistical analysis was done using SPSS 21(SPSS, Chicago, IL, USA).

Statistical significance was set at a 2-sided $P<0.05$.

Results

The Fushimi cohort (n=1,791) had a mean (standard deviation [SD]) age 81.8 (5.3) years and CHA_2DS_2-VASc score 4.3 (1.4), whereas the Darlington cohort (n=1,338) had a mean (SD) age 83.6 (5.7) years and CHA_2DS_2-VASc score 4.4 (1.4). (Table 1, Figure 1) The appropriate use of oral anticoagulation (OAC) was <60% in both registries despite all patients being at a high risk of stroke (i.e., CHA_2DS_2-VASc score≥2).

Over a 12 month follow-up period, observed stroke and mortality rates in Fushimi were 3.4% (n=61) and 11.5% (n=206), whilst corresponding event rates in the Darlington cohort were 4.4% (n=59) and 14.1% (n=188), respectively. The distribution of outcomes, stroke and death, in both registries is described according to CHA_2DS_2-VASc score in Figure 2, where the patterns were broadly comparable.

Figure 3 demonstrates that the proportion of patients receiving OAC varied by stroke risk from 46% with a CHA_2DS_2-VASc score of 2, to 76% with a CHA_2DS_2-VASc of 8 in Fushimi, whereas in Darlington, from 43% with a CHA_2DS_2-VASc score of 2, to 50% with a CHA_2DS_2-VASc of 8. Significant differences were seen in the proportion of patients receiving combination OAC and antiplatelet therapy (APT), and APT alone, both of which rose with increasing CHA_2DS_2-VASc score in the Fushimi cohort, whereas the proportion receiving combination OAC and APT in the Darlington cohort was under 10%, while the proportion on APT alone was as high as 40% across all CHA_2DS_2-VASc scores. The proportion not receiving any antithrombotic therapy was relatively high among patients with a lower CHA_2DS_2-VASc score in Fushimi when compared with those in Darlington cohort.

On multivariable logistic regression analysis (Table 2), an increased risk of stroke was independently associated with previous stroke (Odds Ratio [OR] 2.96, 95%CI 2.01-4.35; p<0.001), but not ethnicity (OR 0.92, 95%CI 0.63-1.36; p=0.69).

A lower risk of death was independently associated with OAC use (OR 0.53, 95%CI 0.41-0.67; p<0.001) and positively associated with age (OR 1.10, 95%CI 1.08-1.12; p<0.001) and heart failure (OR 1.71, 95%CI 1.35-2.15; p<0.001), previous stroke (OR 1.33, 95%CI 1.03-1.71; p=0.03) and vascular disease (OR 2.14, 95%CI 1.63-2.79; p<0.001).

Sub-group analysis

A sub-group analysis of 1,489 elderly patients (aged≥75) without OAC use, from the Fushimi AF Registry (n=798) and the Darlington AF Registry (n=691), was performed. In the Fushimi AF registry, mean (SD) age was 82.9 (5.9) years and mean (SD) CHA_2DS_2-VASc score was 4.2 (1.3). Corresponding figures for the Darlington AF registry were 85.0 (6.0) years and 4.3 (1.4), respectively (Supplemental Table I).

Among these patient, 65 patients experienced stroke (n=31; 3.9%/year in Fushimi vs. n=34; 4.9%/year in Darlington) over the 12 month follow-up period. The incidence of all-cause mortality was 15.5% (n=124) in Fushimi and 19.4% (n=134) in Darlington (Supplemental Table II).

On multivariable analysis of the sub-group data, a history of stroke (OR 2.42; 95%CI 1.39–4.12; p=0.002) was associated with the risk of stroke, but not ethnicity (Japan vs. UK) (OR 0.86; 95%CI 0.50-1.47; p=0.58) [Table 3]. The risk of death was independently associated

with age (OR 1.10; 95%CI 1.07-1.13; p<0.001), heart failure (OR 1.64; 95%CI 1.20-2.24; p=0.002), a history of stroke (OR 1.62; 95%CI 1.14-2.27; p=0.01) and vascular disease (OR 2.36; 95%CI 1.64-3.37; p<0.001) but was lowered with use of antiplatelet agents (OR 0.39; 95%CI 0.28-0.54; p<0.001), and with Japanese ethnicity (Japan vs. UK) (OR 0.67; 95%CI 0.49-0.92; p=0.01).

Discussion

In this analysis, which compared elderly (age≥75) AF patients in both Japan and the UK for the first time, both registry cohorts are at similarly high risk of stroke and death. Second, OAC was under-utilised (<60%) in both populations, despite a lower risk of death being significantly associated with OAC use. Third, ethnicity (Japanese vs. British) was not independently associated with the risk of stroke after adjustment for potential confounders that could influence the risk of events regardless of whether or not OAC was used.

Ethnic differences

The age-adjusted prevalence of AF may be lower among Asians than among Caucasians. [7] However, the risk of stroke and systemic embolism for warfarin-anticoagulated AF Asian patients appears higher compared to non-Asians, though Asians had similar mean stroke risk scores. [8 9]

In the present comparative study, the incidence of stroke in elderly patients (aged≥75) in Japan was 3.4% and 4.4% in the UK. In sub-group analysis of elderly patients not receiving OAC, the same trends were found (3.9% in Japan vs. 4.9% in the UK). Importantly, multivariable analysis showed that ethnicity was not independently associated with the risk of stroke, after adjustment for potential confounders (i.e., the components of CHA_2DS_2-VASc score). Thus, there is no obvious racial difference between Japan and the UK in the risk of stroke amongst elderly AF patients.

Current use of antithrombotic therapy

In recent years in Japan, prescription of warfarin has increased up to approximately 73% without any gender differences.[10,11] The high rate of warfarin use in these cohorts may reflect the participation in the selected institutions with cardiologists who are more familiar with anticoagulation treatment in AF. In the present community based study, OAC therapy was still underutilised (<60%) in both Japanese and British elderly populations. The risks are probably multifactorial, perhaps reflecting a perception that elderly patients with AF have carry a relatively higher risk of major bleeding, but the relative benefits/harms of oral anticoagulation for stroke or mortality and major bleeding showed consistency despite increasing age strata in a real-world and clinical trial setting.[12 13]

Recent clinical trials[14 15] and guidelines[16] may also have contributed to the decrease in the use of antiplatelet agents in Fushimi registry. Nonetheless, about 40% of patients at high risk of stroke were still receiving antiplatelet monotherapy in the Darlington registry. Although the present analysis did not capture the reasons for withholding antithrombotic therapy, other registries [17] found that more than half of reasons reported were based on physician choice (that is, fears over the risk of bleeding and/or falls, worries over patient adherence). A recent analysis of elderly patients from the UK General Practice Research Database (GPRD) [18] suggested that the under-utilisation of OAC among this group was not a result of bleeding risk or comorbidities. Therefore, this may highlight the importance of determining individual stroke and bleeding risk and discussing treatment options with patients, prior to considering OAC therapy in elderly patients.

Limitations

First, our study showed the risk of death was inversely related to OACs use, but this might be reflected by the fact that OACs were unlikely to be used in patients with poorer general health status (i.e., shorter life expectancy). The aspirin effect may be due to the reduction of *cardiovascular disease* morbidity and mortality (where aspirin has some benefit overall, albeit modest), rather than stroke/thromboembolism reduction (where aspirin has virtually no beneficial effect)[19]. This small mortality effect of aspirin (but with no impact on stroke) was also seen recently in a paper from the Danish registries[20]. In addition, OAC treatment in the randomised trials is associated with a significant reduction in all cause mortality (by 26%), compared to placebo or control[21]. Second, despite adjustment for various risk factors, there remains the potential for residual confounding. For instance, a significant association between ethnicity and death in the pooled sub-group analysis may be the result of confounding that cannot be mitigated by statistical adjustment. The fact that patients in Japanese population are younger than those in the UK may have a beneficial impact on mortality in these populations. Third, compared with the UK patients, the use of combination therapy of OAC with antiplatelet agents was three fold higher in Japanese patients. Although OACs are recommended as effective stroke prevention in routine clinical practice in Japan, anti-platelet drugs are likely to be overused. [4] No comparative data are available on the bleeding risk of the 2 cohorts due to the lack of data on bleeding complications in the UK registry, and further inter-ethnic studies are needed to investigate the association between the use of combination therapy and bleeding risks in different ethnic groups.

Fourth, data regarding warfarin control level (i.e., time in therapeutic range) was not available in the Darlington registry during the follow-up period. Thus, to exclude the

possible influence of OAC use on outcomes, we performed the sub-group analysis in patients not receiving OAC, and evaluated racial difference between Japan and the UK in the risk of stroke. Fifth, even though Fushimi-ku and Darlington regions are relatively densely populated urban areas, and is assumed to represent a typical urban community in their respective countries, the results in each region cannot completely represent that situation in the 2 countries as a whole. Last, the present analysis did not capture the reasons for withholding antithrombotic therapy, bleeding problems or compliance issues. These may potentially be linked to the incidence of stroke and worsening prognosis.

In conclusion, elderly (age≥75) AF patients in both Japan and the UK are at similarly high risk of stroke and death, but OAC is still under-utilised in both populations. Ethnicity was not independently associated with the risk of stroke in elderly AF patients, regardless of whether OAC was used or not.

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Figure legends

Figure 1: CHA_2DS_2-VASc score distribution between patients with atrial fibrillation in Japan and the United Kingdom

Figure 2: Stroke and death rate over 1 year follow-up for patients with atrial fibrillation in Japan and the United Kingdom

Figure 3: Anti-thrombotic therapies in patients with atrial fibrillation by CHA_2DS_2-VASc score

Table 1: Patient characteristics and current use of anti-thrombotic therapies in the Japanese and United Kingdom cohorts

	Fushimi AF registry (Japan)	Darlington AF registry (UK)	P value
Total (n=)	1791	1338	
Mean (SD) Age, years	81.8 (5.3)	83.6 (5.7)	<0.01
Female (%)	887 (49.5)	739 (55.2)	<0.01
Hypertension (%)	1141 (63.7)	934 (69.8)	<0.01
Diabetes Mellitus (%)	400 (22.3)	288 (21.5)	0.59
Heart failure (%)	600 (33.5)	351 (26.2)	<0.01
Previous stroke (%)	424 (23.7)	307 (22.9)	0.63
Vascular disease (%)	215 (12.0)	270 (20.2)	<0.01
Mean (SD) $CHADS_2$ score	2.7 (1.2)	2.6 (1.2)	0.43
Mean (SD) CHA_2DS_2-VASC score	4.3 (1.4)	4.4 (1.4)	0.03
Medication			
Oral anticoagulants	993 (55.4)	647 (48.4)	<0.01
- Vitamin K antagonist	902 (50.4)	634 (47.4)	0.10
- Non-vitamin K antagonist	91 (5.1)	13 (1.0)	<0.01
Antiplatelet agents	597 (33.3)	585 (43.7)	<0.01
Combination use of Oral anticoagulants and Antiplatelet agents	270 (15.1)	63 (4.7)	<0.01
No antithrombotic agents	471 (26.3)	169 (12.6)	<0.01

SD, standard deviation; UK, United Kingdom; AF, atrial fibrillation

$CHADS_2$ score, Congestive heart failure, Hypertension, Age ≥ 75 years, Diabetes mellitus, and previous stroke/transient ischemic attack (double);

CHA_2DS_2-VASc score, Congestive heart failure, Hypertension, Age ≥ 75 years (double), Diabetes mellitus, previous thromboembolism (double), Vascular disease, Age 65–74 years, and female gender

Table 2: Multivariate logistic regression analysis for stroke and death

	Stroke		**Death**	
	OR (95%CI)	P value	OR (95%CI)	P value
Age	1.03 (0.99-1.06)	0.11	1.10 (1.08-1.12)	<0.001
Female	1.36 (0.91-2.04)	0.13	1.02 (0.81-1.29)	0.86
Heart failure	0.97 (0.63-1.46)	0.88	1.71 (1.35-2.15)	<0.001
Hypertension	1.26 (0.83-1.94)	0.29	0.90 (0.71-1.14)	0.36
Diabetes mellitus	1.21 (0.77-1.84)	0.40	1.12 (0.85-1.45)	0.42
Previous stroke	2.96 (2.01-4.35)	<0.001	1.33 (1.03-1.71)	0.03
Vascular disease	1.24 (0.74-1.99)	0.41	2.14 (1.63-2.79)	<0.001
Use of oral anticoagulation	0.69 (0.46-1.02)	0.06	0.53 (0.41-0.67)	<0.001
Ethnicity* (Japan vs UK)	0.92 (0.63-1.36)	0.69	1.01 (0.80-1.27)	0.92

* UK as a reference

OR, Odds Ratio; CI, Confidence Interval; UK, United Kingdom

Table 3: Multivariate logistic regression analysis for stroke and death in patients not receiving oral anticoagulation (n=1489; Japan from Fushimi AF Registry [n=798] and the UK from Darlington AF Registry [n=691])

	Stroke		**Death**	
	OR (95%CI)	P value	OR (95%CI)	P value
Age	0.99 (0.95-1.03)	0.68	1.10 (1.07-1.13)	<0.001
Female	1.59 (0.93-2.79)	0.09	1.10 (0.81-1.49)	0.54
Heart failure	1.04 (0.57-1.83)	0.89	1.64 (1.20-2.24)	0.002
Hypertension	1.53 (0.87-2.84)	0.14	0.81 (0.60-1.10)	0.18
Diabetes mellitus	1.47 (0.82-2.53)	0.19	1.17 (0.81-1.65)	0.40
Previous stroke	2.42 (1.39-4.12)	0.002	1.62 (1.14-2.27)	0.01
Vascular disease	1.29 (0.65-2.39)	0.45	2.36 (1.64-3.37)	<0.001
Use of antiplatelet agents	1.20 (0.68-2.15)	0.54	0.39 (0.28-0.54)	<0.001
Ethnicity* (Japan vs UK)	0.86 (0.50-1.47)	0.58	0.67 (0.49-0.92)	0.01

* UK as a reference

OR, Odds Ratio; CI, Confidence Interval; UK, United Kingdom

Figure 1: CHA_2DS_2-VASc score distribution between patients with atrial fibrillation in Japan and the United Kingdom

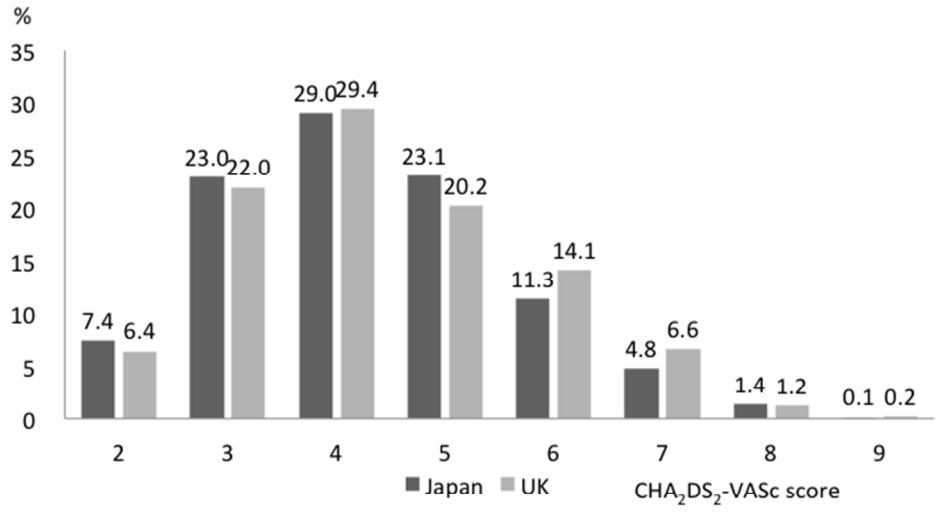
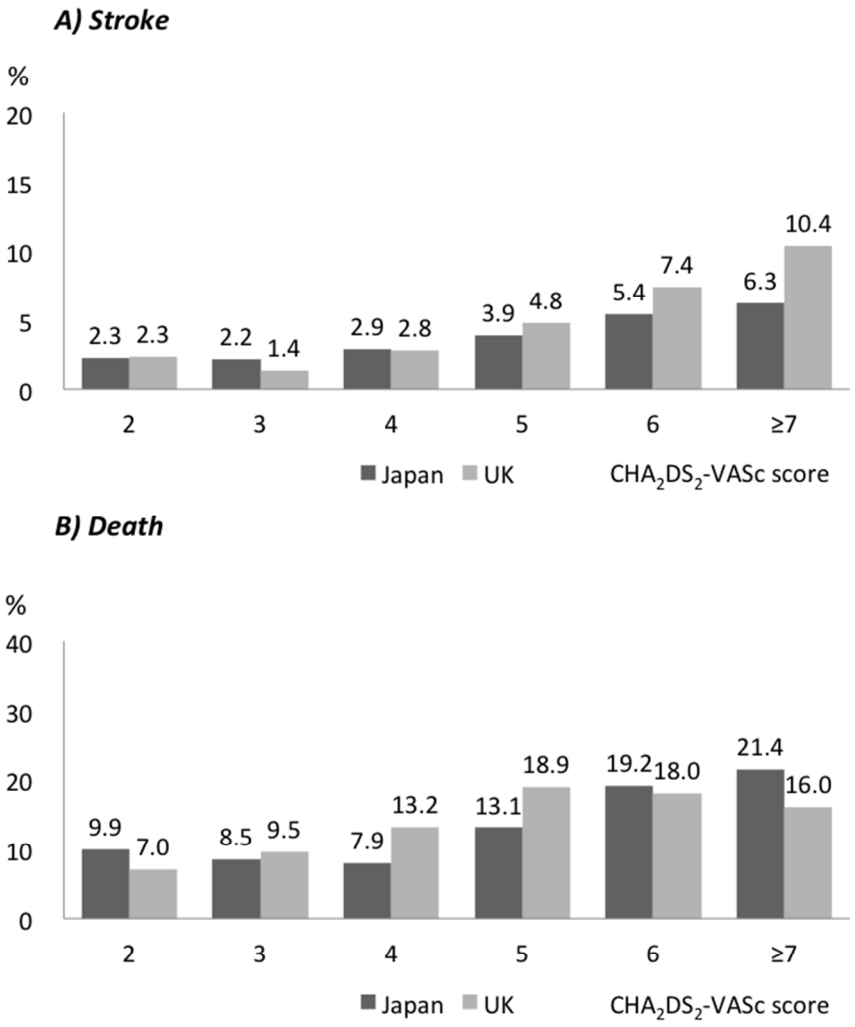


Figure 1
254x190mm (72 x 72 DPI)

Figure 2: Stroke and death rate over 1 year follow-up for patients with atrial fibrillation in Japan and the United Kingdom



Figue 2
254x338mm (72 x 72 DPI)

Figure 3: Anti-thrombotic therapies in patients with atrial fibrillation by CHA_2DS_2-VASc score

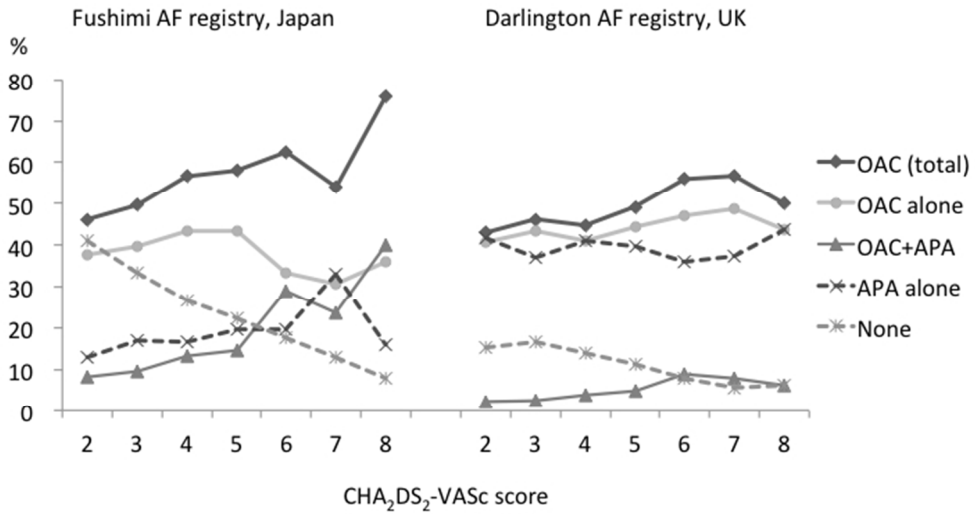


Figure 3
254x190mm (72 x 72 DPI)

STROBE Statement—checklist of items that should be included in reports of observational studies

	Item No	Recommendation	PAGE
Title and abstract	1	(*a*) Indicate the study's design with a commonly used term in the title or the abstract	1
		(*b*) Provide in the abstract an informative and balanced summary of what was done and what was found	3
Introduction			
Background/rationale	2	Explain the scientific background and rationale for the investigation being reported	4
Objectives	3	State specific objectives, including any prespecified hypotheses	4
Methods			
Study design	4	Present key elements of study design early in the paper	5
Setting	5	Describe the setting, locations, and relevant dates, including periods of recruitment, exposure, follow-up, and data collection	5
Participants	6	(*a*) *Cohort study*—Give the eligibility criteria, and the sources and methods of selection of participants. Describe methods of follow-up *Case-control study*—Give the eligibility criteria, and the sources and methods of case ascertainment and control selection. Give the rationale for the choice of cases and controls *Cross-sectional study*—Give the eligibility criteria, and the sources and methods of selection of participants	5
		(*b*) *Cohort study*—For matched studies, give matching criteria and number of exposed and unexposed *Case-control study*—For matched studies, give matching criteria and the number of controls per case	5-6
Variables	7	Clearly define all outcomes, exposures, predictors, potential confounders, and effect modifiers. Give diagnostic criteria, if applicable	5-6
Data sources/ measurement	8*	For each variable of interest, give sources of data and details of methods of assessment (measurement). Describe comparability of assessment methods if there is more than one group	*5-6*
Bias	9	Describe any efforts to address potential sources of bias	
Study size	10	Explain how the study size was arrived at	
Quantitative variables	11	Explain how quantitative variables were handled in the analyses. If applicable, describe which groupings were chosen and why	6
Statistical methods	12	(*a*) Describe all statistical methods, including those used to control for confounding	6
		(*b*) Describe any methods used to examine subgroups and interactions	6
		(*c*) Explain how missing data were addressed	
		(*d*) *Cohort study*—If applicable, explain how loss to follow-up	

was addressed

Case-control study—If applicable, explain how matching of cases and controls was addressed

Cross-sectional study—If applicable, describe analytical methods taking account of sampling strategy

(*e*) Describe any sensitivity analyses

Continued on next page

Results			Page
Participants	13*	(a) Report numbers of individuals at each stage of study—eg numbers potentially eligible, examined for eligibility, confirmed eligible, included in the study, completing follow-up, and analysed	7
		(b) Give reasons for non-participation at each stage	
		(c) Consider use of a flow diagram	
Descriptive data	14*	(a) Give characteristics of study participants (eg demographic, clinical, social) and information on exposures and potential confounders	7
		(b) Indicate number of participants with missing data for each variable of interest	
		(c) *Cohort study*—Summarise follow-up time (eg, average and total amount)	
Outcome data	15*	*Cohort study*—Report numbers of outcome events or summary measures over time	*7*
		Case-control study—Report numbers in each exposure category, or summary measures of exposure	
		Cross-sectional study—Report numbers of outcome events or summary measures	
Main results	16	(*a*) Give unadjusted estimates and, if applicable, confounder-adjusted estimates and their precision (eg, 95% confidence interval). Make clear which confounders were adjusted for and why they were included	7-8
		(*b*) Report category boundaries when continuous variables were categorized	
		(*c*) If relevant, consider translating estimates of relative risk into absolute risk for a meaningful time period	
Other analyses	17	Report other analyses done—eg analyses of subgroups and interactions, and sensitivity analyses	
Discussion			
Key results	18	Summarise key results with reference to study objectives	10
Limitations	19	Discuss limitations of the study, taking into account sources of potential bias or imprecision. Discuss both direction and magnitude of any potential bias	12
Interpretation	20	Give a cautious overall interpretation of results considering objectives, limitations, multiplicity of analyses, results from similar studies, and other relevant evidence	12
Generalisability	21	Discuss the generalisability (external validity) of the study results	12
Other information			
Funding	22	Give the source of funding and the role of the funders for the present study and, if applicable, for the original study on which the present article is based	1

*Give information separately for cases and controls in case-control studies and, if applicable, for exposed and unexposed groups in cohort and cross-sectional studies.